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Beneficial effect of early infusion of landiolol, a very short-acting beta-1 adrenergic receptor blocker, on reperfusion status in acute myocardial infarction

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ABSTRACT

Background: An early IV beta blocker during primary percutaneous coronary intervention (PCI) has been shown to reduce infarct size in ST-segment elevation acute myocardial infarction (STEMI), although the underlying mechanism is unknown. The aim of this study was to investigate the efficacy of early infusion of landiolol, the short-acting beta-1 adrenergic receptor blocker, on the reperfusion status in a STEMI.

Methods: We conducted a prospective, single-group trial of landiolol during the primary PCI for a STEMI. Landiolol was started intravenously just before reperfusion. The reperfusion status and outcomes in 55 treated patients were compared with those in 60 historical controls treated without landiolol. The optimal reperfusion was assessed by an ST-segment resolution (STR), coronary flow, and myocardial brush grade (MBG) after reperfusion.

Results: Patients in the landiolol group achieved a higher rate of an STR (64% vs. 42%, $p = 0.023$) and MBG 2/3 (64% vs. 45%, $p = 0.045$), whereas coronary flow was comparable between the two groups. A multivariate analysis showed that landiolol use was an independent predictor of an STR (odds ratio 2.99, 95% confidence interval 1.25–7.16, $p = 0.014$). The incidence of non-sustained ventricular tachycardia (27% vs. 50%, $p = 0.014$), hypotension (15% vs. 32%, $p = 0.046$), and progression to Killip class grade III or IV (0% vs. 10%, $p = 0.028$) were lower in the landiolol group.

Conclusion: Early infusion of landiolol during the primary PCI was associated with optimal reperfusion and a lower incidence of adverse events in comparison with the control group.

1. Introduction

In the era of a primary PCI for a STEMI, the early salvage of infarcted myocardium has become a matter of concern. Ibanez et al. and Pizarro et al. reported that early intravenous metoprolol before reperfusion reduced infarct size and incidence of severe left ventricular systolic dysfunction [1,2]. However, the underlying mechanism remains to be investigated, although attenuated reperfusion injury and reduced myocardial oxygen consumption have been proposed as two major potential mechanisms [3]. There have been not enough clinical evidences to demonstrate these mechanisms.

Metoprolol is a widely used beta blocker with a cardio-selectivity (β1/β2) of 70 and a half-life of 3–4 h [4]. However, when performing a primary PCI in patients with a STEMI, their blood pressures and heart rates dramatically change every few minutes. Accordingly, the safety of metoprolol for those patients remains to be under consideration. Landiolol hydrochloride has been recognised as a novel agent

Abbreviations: ACS, Acute coronary syndrome; AV block, Atrioventricular block; CCU, Coronary care unit; CK, Creatinine kinase; MB, Myoglobin binding; PCI, Percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; STR, ST-segment resolution; SYNTAX, SYNergy between PCI with TAXUS™ and Cardiac Surgery; TIMI, thrombolysis in myocardial infarction; VT, Ventricular tachycardia.

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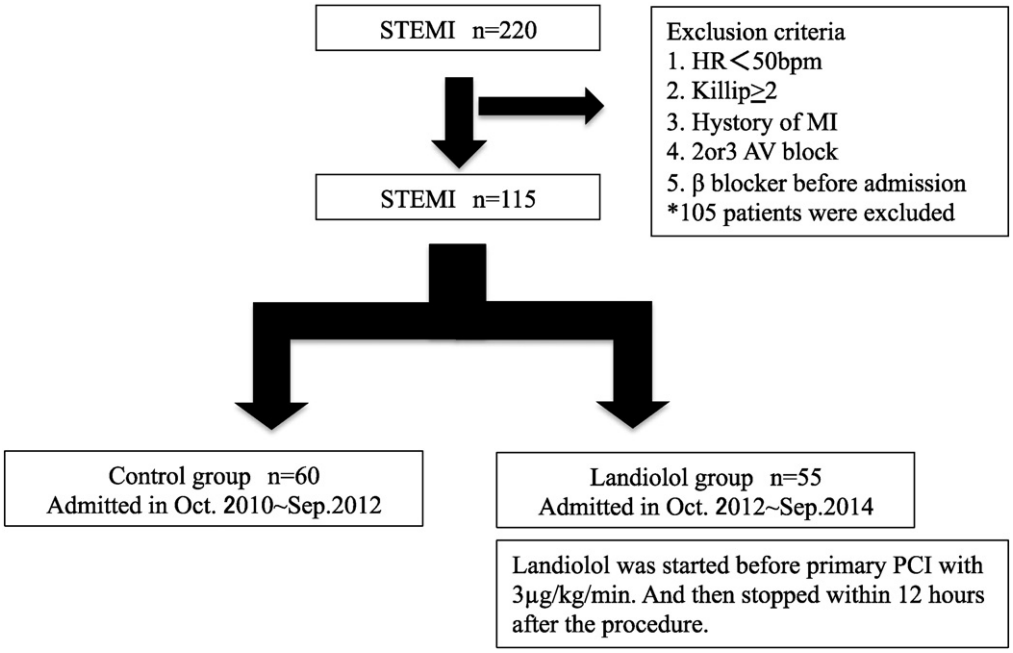

Fig. 1. Flow diagram of this study. AV, atrioventricular; HR, heart rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

developed in Japan and is characterised by a higher cardio-selectivity ($\beta1/\beta2 = 225$) and shorter half-life (4 min) than metoprolol [5]. For this reason, landiolol can be an alternative agent to metoprolol with less concern for the adverse effects of metoprolol. The purpose of this study was to investigate the safety and efficacy of early infusion of landiolol on the reperfusion status in a STEMI.

2. Methods

2.1. Study population

The present study is a prospective, single-group trial of early infusion of landiolol during a primary PCI for a STEMI. A (See Fig.1.) total of 55 consecutive Japanese patients who presented between October 2012 and September 2014 were enrolled (landiolol group). The reperfusion status and clinical outcomes in these patients were compared with a historical control cohort of 60 consecutive Japanese patients who presented between October 2010 and September 2012 without landiolol treatment (control group). Patients with a heart rate < 50 beats/min, Killip class grade II or greater, 2 or 3 AV block on admission, history of myocardial infarction, and oral beta blocker use before admission were excluded. A STEMI was diagnosed when the patient had been admitted with chest pain that had lasted for 30 min with an ST-segment elevation of ≥0.2 mV in at least two contiguous leads and an elevation of CK or its MB isozyme to at least twice the normal levels [6]. The ethical committee of our institution approved the present study, and all patients provided written informed consent (UMIN000021668).

2.2. PCI procedure and assessment

All patients received 200 mg of aspirin, a 300-mg loading dose of clopidogrel, and 70–100 U/kg of intravenous unfractionated heparin before the PCI. Glycoprotein IIb/IIIa inhibitors were not available in Japan at the time of this study. Thrombus aspiration was performed on all patients just after passing the guide wire through the culprit legion. The use of a distal protection device before the balloon inflation and the stent implantation was left to the physician's discretion. All patients underwent a PCI according to the current guidelines. A SYNTAX score was calculated as previously reported [7]. A myocardial blush grade was assessed at the end of the procedure using the densitometric method [8].

2.3. Landiolol

In the landiolol group, an intravenous infusion of landiolol (Ono Pharmaceutical Co., Ltd., Osaka, Japan) was started just before reperfusion with 3 μg/kg/min [9]. This dose was continued during and after the PCI procedure and then stopped within 6–12 h after the primary PCI. An unscheduled discontinuation of landiolol was left to the physician's discretion.

2.4. Endpoints

The efficacy endpoint was a reperfusion status assessed by an STR, myocardial blush grade, and thrombolysis in myocardial infarction (TIMI) flow grade. An STR was defined as more than 70% of a resolution of the sum of an ST-segment elevation between the time of admission and just after the primary PCI [10,11]. The sum of an ST-segment elevation was calculated in leads I, aVL, and V1–V6 for an anterior STEMI and in leads II, III, aVF, and V5–V6 for a nonanterior STEMI. The ST-segment elevation was measured to the nearest 0.025 mV, 20 milliseconds after the end of the QRS using the isoelectric line [10]. The isoelectric line was defined as the level of the preceding TP segment. We considered an STR as optimal myocardial reperfusion, which has been previously described [12–14].

The safety endpoint was adverse events during admission and within 12 months after the discharge. Adverse events during admission were defined as hypotension or bradycardia at the end of reperfusion, death within 24 h, death during admission, progression to Killip class grade III or greater during admission, reinfarction during admission, 2 or 3 degrees of AV block, cardiogenic shock, ventricular fibrillation/sustained VT, hypotension, bradycardia, and non-sustained VT within 24 h after a PCI [1]. Hypotension was defined as systolic blood pressure < 90 mm Hg. Bradycardia was defined as a heart rate < 50 beat/min. Cardiogenic shock was defined as the presence of hypotension with the physician's discretion of requiring inotropic agents. Adverse events after discharge were defined as cardiac death, non-fatal myocardial infarction, non-fatal stroke, heart failure requiring hospitalisation, and target vessel revascularisation within 12 months after discharge.

2.5. Statistical analysis

Data were expressed as mean values ± standard deviation (SD) or median (interquartile range) for the continuous variables and as percentages for the categorical variables. The continuous variables were compared using a Student's *t*-test or a Mann–Whitney test as appropriate. A chi-square analysis or Fisher's exact test was used to compare the categorical variables. Differences were considered statistically significant at $p < 0.05$. A multivariate logistic regression analysis with a backward selection, with an output criterion of $p > 0.10$, was used to identify clinical predictors of STR among the variables significantly ($p < 0.05$) associated with this index according to a univariate logistic regression analysis. The odds ratios and 95% confidence intervals were calculated. Cumulative 12-month events were compared using a log-rank test. Data were analysed using the SPSS statistical package (Release 22, SPSS Inc., Chicago, IL, USA).

3. Results

The baseline characteristics of the patients are summarised in Table 1. There were no differences between the landiolol group and control group in age, sex, coronary risk factors, and medications before admission. In the landiolol group, the time from admission to the start of landiolol was 35 ± 23 min, and the time from starting landiolol to reperfusion was 33 ± 15 min.